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Kaplan
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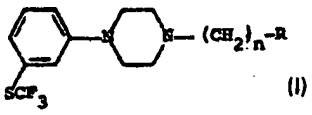
J. A. Kemp & Co

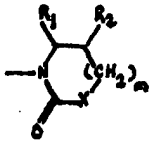
(54) 1-substituted alkyl-4-(3-trifluoromethylthiophenyl)-piperazines

(57) Compounds having the general formula (I)



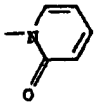
(I)

in which n is 1, 2 or 3 and R represents (i) a group of formula:



(A) in which R_1 and R_2 represent hydrogen atoms or together represent a group of formula:

, thereby completing a benzene ring fused to the heterocyclic ring shown in formula (A), X is a —S—, —O—, imino, alkyl-imino or methylene group and m is 0 or 1, or R represents (ii) a group of formula:



(B), (iii) a 2-tetrahydrofuryl group, (iv) a group of formula $—CH_2—S—Z$, Z representing a hydrogen atom, alkyl group or —CO— alkyl group or (v) a group of formula $—CH_2—O—$ alkyl, having from 1 to 8 carbon atoms, and their pharmaceutically acceptable acid addition salts are useful in therapy, especially for treatment of anxiety and depression.

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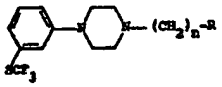
SPECIFICATION

Phenylpiperazine derivatives

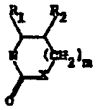
The present invention relates to therapeutically useful phenylpiperazine derivatives.

The phenylpiperazine derivatives of the invention are compounds of the general formula (I)



(I)

in which n is 1, 2 or 3 and R represents (i) a group of formula:



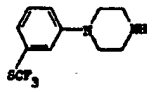
(A) in which R_1 and R_2 represent hydrogen atoms or together represent a group of formula:

thereby completing a benzene ring fused to the heterocyclic ring shown in formula (A), X is a thio, oxy, imino, alkylimino or methylene group and m is 0 or 1, or R represents (ii) a group of formula:

(B),

(iii) a 2-tetrahydrofuryl group, (iv) a group of formula —CH_2—S—Z, Z representing a hydrogen atom, alkyl group or —CO— alkyl group or (v) a group of formula —CH_2—O— alkyl, the alkyl groups having from 1 to 8 carbon atoms, and their pharmaceutically acceptable acid addition salts.

The invention includes a process for the preparation of the compounds (I), which comprises reacting 1-(*m*-trifluoromethylthiophenyl)piperazine (II)



with a compound (III)

$$Y—(CH_2)_n—R \qquad \text{(III)}$$

In which R and n have the meanings given above and Y represents an anion of an activated alcohol derivative, preferably a halide, mesylate, tosylate or halogenomethanesulphonate ion. Alternatively Y can be defined as a leaving atom or group reactive with a secondary amino group.

This reaction can be carried out conveniently at a temperature of 20 to 150°C in a polar or non-polar solvent, e.g. a benzene hydrocarbon, a hydroxylic or ketonic solvent, N,N-dimethylformamide (DMF) or hexamethylphosphorotriamide (HMPT).

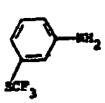
In order to prepare the compound (I) in which n is 1 and R is a —CH_2SH group, it is also possible to react the 1-(*m*-trifluoromethylthiophenyl)piperazine (II) with ethylene sulphide.

It is also possible to prepare the compounds (I) in which R is

(2-tetrahydrofuryl)

—CH_2O-alkyl or —CH_2S-alkyl

by reacting *m*-(trifluoromethylthio)aniline (IV)



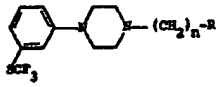
(IV)

SPECIFICATION

Phenylpiperazine derivatives

The present invention relates to therapeutically useful phenylpiperazine derivatives.

The phenylpiperazine derivatives of the invention are compounds of the general formula (I)



(I)

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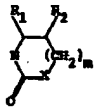


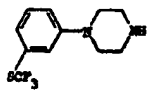
(A) in which R_1 and R_2 represent hydrogen atoms or together represent a group of formula:

thereby completing a benzene ring fused to the heterocyclic ring shown in formula (A), X is a thio, oxy, imino, alkylimino or methylene group and m is 0 or 1, or R represents (ii) a group of formula:

(B),

(iii) a 2-tetrahydrofuryl group, (iv) a group of formula $—CH_2—S—Z$, Z representing a hydrogen atom, alkyl group or —CO— alkyl group or (v) a group of formula $—CH_2—O—$ alkyl, the alkyl groups having from 1 to 8 carbon atoms, and their pharmaceutically acceptable acid addition salts.

The invention includes a process for the preparation of the compounds (I), which comprises reacting 1-(*m*-trifluoromethylthiophenyl)piperazine (II)



with a compound (III)

$$Y—(CH_2)_n—R \qquad \text{(III)}$$

in which R and n have the meanings given above and Y represents an anion of an activated alcohol derivative, preferably a halide, mesylate, tosylate or halogenomethanesulphonate ion. Alternatively Y can be defined as a leaving atom or group reactive with a secondary amino group.

This reaction can be carried out conveniently at a temperature of 20 to 150°C in a polar or non-polar solvent, e.g. a benzene hydrocarbon, a hydroxylic or ketonic solvent, N,N-dimethylformamide (DMF) or hexamethylphosphorotriamide (HMPT).

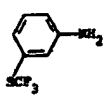
In order to prepare the compound (I) in which n is 1 and R is a $—CH_2SH$ group, it is also possible to react the 1-(*m*-trifluoromethylthiophenyl)piperazine (II) with ethylene sulphide.

It is also possible to prepare the compounds (I) in which R is

(2-tetrahydrofuryl)

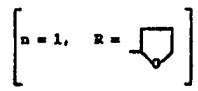
$—CH_2O$-alkyl or $—CH_2S$-alkyl

by reacting *m*-(trifluoromethylthio)aniline (IV)



(IV)

Example 3.
1-(m-Trifluoromethylthio-phenyl)-4-(tetrahydrofuryl-2-methyl)-piperazine and its hydrochloride.



A mixture of 13.5 g (0.05 mol) of (m-trifluoromethylthiophenyl)-piperazine, 13.5 g (0.054 mol) of tetrahydrofuryl-2-methyl tosylate and 13.5 ml of HMPT is heated at 120°C for 2 hours. The mixture is cooled to 10°C and 100 ml of water are added. The oil is separated from the water and then washed 3 times with water in order to remove the HMPT. The oil is taken up in chloroform, the traces of water are separated off and the chloroform solution is dried over magnesium sulphate. A solution of hydrogen chloride in ether is added and the solvents are evaporated off. The evaporation residue is triturated with ether and the precipitate is filtered off. It is rendered alkaline with 2 N NaOH solution and the mixture is extracted with chloroform. The chloroform is evaporated off and the hydrochloride is prepared from the oil remaining after evaporation. The compound is recrystallised from a mixture of isopropanol and ether.

Melting point = 210°C.

Example 4.
1-(m-Trifluoromethylthio-phenyl)-4-(2-mercaptoethyl)-piperazine and its hydrochloride.
[n = 1, R = CH_2SH]

In an Erlenmeyer flask, 3.84 g (0.064 mol) of ethylene sulphide are added dropwise, at 20°C, to a solution of 15 g (0.0557 mol) of (m-trifluoromethylthio-phenyl)-piperazine and 2 ml of methanol.

The mixture is heated gradually to 55°C and this temperature is maintained for 1 hour 30 minutes. The solvent is evaporated off and the residue is rectified in a bulbed tube.

Boiling point = 200°C under a pressure of 0.1 mm Hg.

The hydrochloride is prepared by adding a solution of hydrogen chloride in ether to a solution of the base in ethyl acetate.

Melting point = 141°C.

Example 5.
1-(m-Trifluoromethylthio-phenyl)-4-(2-methylthioethyl)-piperazine and its hydrochloride.
[n = 1, R = CH_3SCH_2]

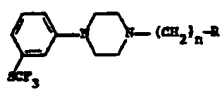
0.84 g (0.0175 mol) of a 50% strength dispersion of sodium hydride is added in portions to a solution, cooled to +5°C, of 4.8 g (0.015 mol) of 1-(m-trifluoromethylthio-phenyl)-4-(2-mercaptoethyl)-piperazine in 40 ml of DMF. When the evolution of hydrogen has ceased, a solution of 2.16 g (0.0152 mol) of methyl iodide in 20 ml of DMF is added dropwise. The reactants are left in contact overnight. The mixture is poured onto ice and the resulting mixture is extracted twice with ether The ether solution is dried over magnesium sulphate and evaporated.

The hydrochloride is prepared in ethyl acetate by adding the theoretical amount of a solution of hydrogen chloride in ethanol.

Melting point = 135°C.

The following table (I) shows the compounds (I) and salts which have been prepared by way of example.

TABLE



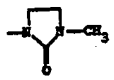
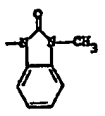
Compound	n	R	Characteristics of the hydrochloride. Melting point (°C)
1	2		188–190 (decomposition)
2	2		217–218 (decomposition)
3	2		230 (decomposition)
4	2		178–180 (decomposition)
5	3		224–227 (decomposition)
6	3		196–199
7 (Example 1)	2		217 –218
8 (Example 2)	2		260–263 (decomposition)

TABLE (Continued)

Compound	n	R	Characteristics of the hydrochloride. Melting point (°C)
9 (Example 3)	1		210
10 (Example 4)	1	$-CH_2SH$	141
11 (Example 5)	1	$-CH_2SCH_3$	135
12	1	$-CH_2OCH_3$	151
13	1	$-CH_2-S-COCH_3$	168
14	1	$-CH_2-O-C_4H_9$	140

The compounds (I) and salts are active in therapy in the field of the central nervous system.

This activity has been demonstrated and measured by the 4 plate test (C. Aron, Thesis in Medicine, Paris 1970; J. R. Boissier, P. Simon and C. Aron, Une nouvelle méthode de détermination des tranquillisants chez la souris. ("A new method for testing tranquillisers in mice"), Eur. J. Pharmacol. 1968, *4*, 145—151).

The compounds are administered orally in several doses (1, 3 and 10 mg/kg), 60 minutes before the test. The percentage disinhibition in the mice is measured.

At a dose of 1 mg/kg, the percentage varies from 35 to 70; at a dose of 3 mg/kg, it varies from 80 to 150 and at a dose of 10 mg/kg, it varies from 120 to 300.

For the same doses, the higher the percentage, the greater is the activity of the compound.

The acute toxicity (LD50) is determined on mice either by intraperitoneal administration after 48 hours or by oral administration for 7 days. The LD50 for intraperitoneal administration varies from 75 to 230 mg/kg. The LD50 for oral administration varies from 250 to 1,000 mg/kg.

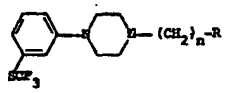
The compounds (I) and salts possess psychotropic properties which permit their use for the treatment of various states of anxiety and of depression.

They can be administered orally or parenterally with any suitable excipient in any suitable form of administration, namely sugar-coated pills, tablets, capsules, dragees, injectable solutions and the like.

The daily posology can range from 5 to 200 mg.

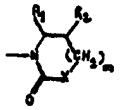
CLAIMS

1. Phenylpiperazine derivatives of the general formula (I)



(I)

in which n is 1, 2 or 3 and R represents (i) a group of formula:



(A)

in which R_1 and R_2 represent hydrogen atoms or together represent a group of formula

thereby completing a benzene ring fused to the heterocyclic ring shown in formula (A), X is —O—, —S— or an imino, alkylimino or methylene group and m is 0 or 1, or R represents (ii) a group of formula:

(B),

(iii) a 2-tetrahydrofuryl group, (iv) a group of formula $—CH_2—S—Z$, Z representing a hydrogen atom, alkyl group or —CO-alkyl group or (v) a group of formula $—CH_2—O$-alkyl, the alkyl groups having from 1 to 8 carbon atoms, and their pharmaceutically acceptable acid addition salts.

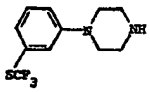
2. Compounds according to claim 1, in which n is 1 and R is a $—CH_2SH$, $—CH_2S$-alkyl, $—CH_2—O$-alkyl or $—CH_2SCO$-alkyl group.

3. Compounds according to claim 2, in which R is a $—CH_2S—CH_3$, $—CH_2—O—CH_3$ or $—CH_2SCOCH_3$ group.

4. Compounds according to claim 1 wherein n and R have the meanings set out in the Table hereinbefore and the pharmaceutically acceptable salts thereof.

5. Compounds according to any preceding claim in the form of hydrochloride salts.

6. A process for the preparation of compounds according to claim 1, which process comprises reacting 1-(*m*-trifluoromethylthiophenyl)piperazine of formula



(II)

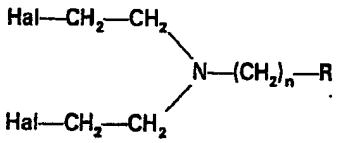
with a compound of formula $R(CH_2)_nY$ (III) in which R and n have the meanings given in claim 1, 2 or 3 and Y represents an anion of an activated alcohol derivative, and if desired converting a free base thereby obtained into a pharmaceutically acceptable acid addition salt.

7. A process according to claim 6 wherein Y represents a halogen atom or a p-toluenesulphonyloxy, methanesulphonyloxy or halogenomethanesulphonyloxy group.

8. A process according to claim 6 or 7 in which the reaction between compounds II and III is effected at a temperature of 20 to 150°C in an organic solvent.

9. A process for the preparation of compounds according to claim 1 in which n is 1 and R is a $—CH_2SH$ group, which process comprises reacting 1-(*m*-trifluoromethylthiophenyl)piperazine with ethylene sulphide, and if desired converting a free base thereby obtained into a pharmaceutically acceptable acid addition salt.

10. A process for the preparation of compounds according to claim 1 in which R is a 2-tetrahydrofuryl, $—CH_2O$-alkyl or $—CH_2S$-alkyl group, which process comprises reacting *m*-(trifluoromethylthio)aniline with a diethylamine derivative of formula



(V)

in which R is as defined above, n is 1, 2 or 3 and Hal represents a halogen atom, and if desired converting a free base thereby obtained into a pharmaceutically acceptable acid addition salt.

11. A process for the preparation of compounds according to claim 1 in which R is a $—CH_2—S$-alkyl or $—CH_2—S—CO$-alkyl group, which process comprises reacting a compound according to claim 1 in which R is a $—CH_2—SH$ group with an alkyl halide or alkylcarbonyl halide in which the alkyl group has from 1 to 8 carbon atoms.

12. A process according to claim 6 substantially as described in Example 1, 2 or 3.

13. A process according to claim 9 substantially as described in Example 4.

14. A process according to claim 11 substantially as described in Example 5.

15. Compounds according to claim 1 when prepared by a process claimed in any one of claims 6 to 14.

16. Pharmaceutical compositions comprising a compound claimed in any one of claims 1 to 5 or in claim 15 in association with a pharmaceutically acceptable excipient.

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